in the aged and poor-risk patient has long been recognized as appropriate and will undoubtedly be more generally adopted. The standard radical mastectomy, as conceived by Halsted, will be used occasionally in the very kind of patient for whom its originator first designed it, the patient with a large, extensive, locally invasive tumor. Early diagnosis should make this a rarity.

Finally, the real hope of tomorrow rests in studies of the type reported in these pages by Gordan and his co-workers. The anti-tumor efficacy of a new testosterone has been clearly shown by the most precise and carefully controlled study. An objective regression rate of 64 percent in far-advanced, hormone-refractory breast carcinoma is an extraordinary contribution. It is to be hoped that this steroid and others like it will soon be widely available. Herein lies immediate and significant new hope for the woman with advanced carcinoma of the breast. Indeed, it seems certain that with early diagnosis and improved hormonal and radiological therapy, there will be an increasing conservatism in the surgical approach to carcinoma of the breast. Many women who only a few years ago would have had a standard radical mastectomy will be treated by local excision or simple mastectomy. We may hope for the day when the biologic features of each tumor can be precisely established and the correct operation selected for each case—local excision for the small early solitary lesion, simple mastectomy for multicentric local lesions, modified radical for a limited number of identifiable stage II tumors without distant metastasis, standard Halsted radical for the rare neglected but localized tumor, and no operation for those who already have occult distant metastatic lesions and whose local lesion and distant lesions can be handled equally well by nonoperative methods.

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New Ideas about Myasthenia Gravis

MYASTHENIA GRAVIS is still with us despite gratifying advances in the management of this melancholy disorder. The three milestones of treatment were reached in the lifetimes of many of us. Mary Walker discovered the efficacy of anticholinesterase drugs in 1934. Thymectomy for myasthenia, pioneered by Blalock in the late 1930's, gained slow acceptance in the following decades. Finally, and of equal importance, came the revolution in management of ventilatory failure in the middle 1950's, partly a result of the introduction of positive pressure ventilation and partly because of increased experience with tracheostomy and tracheobronchial toilette. Nowadays the operative risk of thymectomy is 4 percent or less in experienced hands, and about two-thirds of patients who survive will eventually lead a more or less normal life, many without the aid of anticholinesterase drugs. These results in the more severe cases, combined with the benign prognosis of many milder cases, justify a certain grim optimism about myasthenia in the 1970's.

A great deal of expert and devoted medical care must be expended to achieve results even as good as these, and there remains an appreciable residue of case fatality and chronic disability. Since myasthenia affects about one in 18,000 persons the problem is not negligible. Increasingly, hopes for improved therapy are centering on research into the pathogenesis of the disorders of neuromuscular transmission.

From the neurophysiological studies of Bernard Katz and others,[1] we now know that a nerve impulse releases acetylcholine from presynaptic motor nerve terminals in the form of packets or

quanta. A normal nerve impulse liberates about three hundred quanta, each containing several thousand molecules of acetylcholine. The packets of chemical transmitter, which seem to correspond to the synaptic vesicles seen in electron micrographs, also "leak" spontaneously from the nerve terminals, producing minute depolarizations known as miniature end-plate potentials (mepps). Using similar microelectrode techniques, Elmqvist and his colleagues in Sweden discovered a striking abnormality in human myasthenia gravis: the amplitude of spontaneous mepps was one-fifth of normal, although their frequency was normal. The number of quanta released by a nerve impulse was also normal, but since the quanta themselves were small the amplitude of the end-plate potentials (number released x amplitude of quanta) was often too small to initiate a muscle action potential.[2] The margin of safety for neuromuscular transmission was very small.

This sort of defect could arise in two ways. Either the post-synaptic membrane is insensitive to acetylcholine (as in curare block), or the amount of acetylcholine in each packet is reduced. For many years there was comfortable agreement that the transmission defect in myasthenia is curare-like, post-synaptic; but Elmqvist and others now maintain that the presynaptic hypothesis is correct. The evidence for this is indirect; in their *in vitro* studies the Swedish group was unable to detect any abnormality of the post-synaptic response to chemical analogues of acetylcholine. By this view myasthenia may be a defect in the synthesis or "packaging" of acetylcholine, or a false transmitter may be formed in its place. The closest physiological model of this situation, though not precisely identical, is poisoning by hemicholinium, a chemical which impedes acetylcholine synthesis by blocking the entry of choline into nerve endings. Looking for a hemicholinium-like substance in myasthenia would be a reasonable line for future investigation.

A quite different disturbance of neuromuscular transmission is caused by botulinum toxin and by a group of antibiotics including streptomycin and neomycin. These drugs interfere with the ability of a nerve impulse to release packets of acetylcholine from the nerve endings. Apparently enough quanta are present and each quantum contains a normal amount of acetylcholine, but the number of quanta released by a nerve impulse is very small, and the resulting end-plate potential may again be too small to excite a muscle spike. A similar physiological disturbance occurs in the "myasthenic syndrome" of Eaton and Lambert, sometimes associated with bronchogenic carcinoma.[3] Elsewhere in this issue, Herrmann has reviewed the contrasting clinical features of the two types of naturally-occurring myasthenic disease. There is a surprisingly good correlation between the neurophysiological and the clinical attributes of these different disorders. In the Eaton-Lambert syndrome, for instance, the probability of quantal release can be improved by repetitive nerve stimulation or by use of the drug guanidine hydrochloride; clinically, the hand grip improves after a few seconds of persistent effort, and guanidine is often efficacious. In myasthenia gravis, on the other hand, neuromuscular blockade worsens with repetitive nerve action (the Jolly effect), partly because of a normal phenomenon—Wedensky inhibition; quanta are released faster than they can be replaced. The clinical counterpart of this is the well-known abnormal fatiguability of myasthenic strength. (Desmedt has pointed out that there is an additional abnormality in myasthenia, post-activation exhaustion, which lasts much longer than Wedensky inhibition and indicates that synthesis of acetylcholine may be abnormally slow.[4])

Although there has been some progress in unraveling the disordered physiology of the myasthenic end-plate, the proximate causes are still obscure. Any hypothesis about myasthenia must come to grips with the thymus gland, and two different roles for this organ have now been proposed. Simpson suggested that myasthenia is an autoimmune disease in which the thymus produces antibodies against the motor end-plate. In the same year (1960) Strauss et al discovered muscle antibodies in the serum of some myasthenic patients, but for several reasons these antibodies do not qualify for the role proposed by Simpson. They are detectable in only a third of myasthenic patients without thymoma; they react with cross-striations of muscle (and with myoid cells in the thymus) but not with any portion of the synaptic region; they are present in the serum of almost all myasthenic patients with thymoma, but also in a fourth of cases where thymoma is present without myasthenia.[5]

Goldstein has championed the novel view that

the thymus in myasthenia is itself the victim of an autoimmune process – "thymitis" – which releases a humoral substance causing neuromuscular block. This substance is considered to be a normal constituent of thymus rather than an antibody. (In this context muscle antibodies are epiphenomena resulting from the coincidental presence of primitive muscle-like cells in the thymus, so that some antibodies against thymus also react with muscle.) Goldstein and his colleagues have provided interesting experimental evidence which indirectly supports the idea that damage to the thymus by autoimmune mechanisms may lead to altered neuromuscular transmission.[6] There are, however, two objections which have not been fully answered. One is the incomplete success of thymectomy in curing myasthenia. The other is the occurrence, in 15 reported cases, of myasthenia months or years after apparently total removal of a benign thymoma.[7] Clearly the thymus has not yet unlocked all its secrets.

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A New Ethic for Medicine And Society

THE TRADITIONAL WESTERN ETHIC has always placed great emphasis on the intrinsic worth and equal value of every human life regardless of its stage or condition. This ethic has had the blessing of the Judeo-Christian heritage and has been the basis for most of our laws and much of our social policy. The reverence for each and every human life has also been a keystone of Western medicine and is the ethic which has caused physicians to try to preserve, protect, repair, prolong and enhance every human life which comes under their surveillance. This traditional ethic is still clearly dominant, but there is much to suggest that it is being eroded at its core and may eventually even be abandoned. This of course will produce profound changes in Western medicine and in Western society.

There are certain new facts and social realities which are becoming recognized, are widely discussed in Western society and seem certain to undermine and transform this traditional ethic. They have come into being and into focus as the social by-products of unprecedented technologic progress and achievement. Of particular importance are, first, the demographic data of human population expansion which tends to proceed uncontrolled and at a geometric rate of progression; second, an ever growing ecological disparity between the numbers of people and the resources available to support these numbers in the manner to which they are or would like to become accustomed; and third, and perhaps most important, a quite new social emphasis on something which is beginning to be called the quality of life, a something which becomes possible for the